

Recapitulation of premature ageing with iPSCs from Hutchinson-Gilford progeria syndrome.

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Public Summary:

Hutchinson-Gilford progeria syndrome (HGPS) is a rare and fatal human premature ageing disease, characterized by premature arteriosclerosis and degeneration of vascular smooth muscle cells (SMCs). HGPS is caused by a single point mutation in the lamin A (LMNA) gene, resulting in the generation of progerin, a truncated splicing mutant of lamin A. Accumulation of progerin leads to various ageing-associated nuclear defects including disorganization of nuclear lamina and loss of heterochromatin. Here we report the generation of induced pluripotent stem cells (iPSCs) from fibroblasts obtained from patients with HGPS. HGPS-iPSCs show absence of progerin, and more importantly, lack the nuclear envelope and epigenetic alterations normally associated with premature ageing. Upon differentiation of HGPS-iPSCs, progerin and its ageing-associated phenotypic consequences are restored. Specifically, directed differentiation of HGPS-iPSCs to SMCs leads to the appearance of premature senescence phenotypes associated with vascular ageing. Additionally, our studies identify DNA-dependent protein kinase catalytic subunit (DNAPKcs, also known as PRKDC) as a downstream target of progerin. The absence of nuclear DNAPK holoenzyme correlates with premature as well as physiological ageing. Because progerin also accumulates during physiological ageing, our results provide an in vitro iPSC-based model to study the pathogenesis of human premature and physiological vascular ageing.

Scientific Abstract:

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